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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,344	04/27/2000	Claude Negrier	06478.1442	2949

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FINNEGAN, HENDERSON, FARABOW, GARRETT &
DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20006

EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/559,344	Applicant(s) NEGRIER ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 17, 2002 has been entered.

Status of the Claims

The Amendment filed September 17, 2002 has been entered and considered. Claims 1-14 are pending.

Drawings

The drawings have been approved by the draftsperson.

Rejections Withdrawn

The rejection of Claim 12 under 35 U.S.C. 112, second paragraph is withdrawn in light of the amendment to the claim.

The rejection of Claims 2-4, 8, 13, and 14 under 35 U.S.C. 112, second paragraph as improperly dependent because platelets are not hematopoietic cells is withdrawn in light of the amendments to the claims.

The rejection of Claims 2-4, 8, 13, and 14 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in light of the amendments to the claims.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "DNA coding for the human platelet glycoprotein IIb promoter " is still unclear (see p. 2, line 2 of paragraph numbered 3 in the Office Action) because DNA sequences do not "code" for promoters. Rather, promoters are specific DNA sequences to which the transcription complex binds. The examiner suggests amending the claim to read "the DNA sequence for the human platelet glycoprotein IIB promoter" as has been done in amended Claim 12.

Therefore, the rejection of Claim 2 is maintained. Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al. (Human Gene Therapy (July 1995) 6: 873-880) in view of Uzan et al. (J. Biol. Chem. (1991) 266(14): 8932-8939).

It is noted that the new claims added to this rejection are necessitated by the amendment changing the limitation that the cells were platelets (not taught in the prior art) to the present limitation that the cells are megakaryocytes (taught in Uzan et al.).

The rejection is restated below followed by a response to Applicants arguments.

Hao et al. teaches a DNA construct for the expression of *factor IX* in a *hematopoietic* cell line (HL-60 cells; p. 877, Col. 2) comprising DNA coding for a blood coagulation factor (FIX) and a process of using the construct to express factor IX in a hematopoietic cell line (HL-60; see abstract). Hao et al. suggests *using hematopoietic-specific promoters* (p. 879, Col. 1, lines 27-28). Hao et al. also *teaches induction of expression with PMA* in HL-60 cells (p. 878, Table I).

Hao et al. does not teach specifically using the GPIIb promoter but does suggest using hematopoietic specific promoters to express factor IX in general.

Uzan et al. provides a characterization of the *GPIIb promoter* and concludes that the GPIIb promoter contains sufficient information to direct tissue specific expression and suggests that this promoter can be used to target expression of heterologous genes in *megakaryocytes* (hematopoietic cells; see p. 8932, 1st paragraph of intro. And p. 8938, Col. 2, last two lines).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the DNA construct for the expression of factor IX as taught in Hao et al. such that it contained the hematopoietic specific promoter, GPIIb, characterized in Uzan et al. and use the DNA construct in a method of making factor IX as taught in Hao et al. One would have been motivated to make such a DNA construct and use it to produce Factor IX because Hao et al. teaches that DNA constructs comprising a hematopoietic-specific promoter and a sequence coding for Factor IX are desirable for potential use in transfecting hematopoietic cells to be used in the treatment of hemophilia because they are more readily obtained than other cells, such as hepatocytes (see p. 878, Discussion, paragraph bridging Col. 1 and 2). Thus, it appears that the claims are unpatentable over the prior art.

Applicants argue that one skilled in the art would not be motivated to use a cell lineage specific promoter in conjunction with the DNA construct disclosed in Hao et al. because Hao et al. does not disclose any data regarding cell lineage specific promoters such as the GPIIb promoter and that direction of gene expression to megakaryocytes is

not mentioned in Hao et al. In addition, Applicants argue that the suggestion of Hao et al. to use hematopoietic-specific promoters is only a "general incentive to try" a hematopoietic specific promoter and that "obvious to try" is not the standard of obviousness. This argument has been considered but is not deemed persuasive because Applicant appears to be arguing against the references individually and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The ultimate goal of the Hao et al. research is to engineer a cell to produce and secrete sufficient levels of a functional clotting factor that could act as a continuous in vivo source. As part of this research, Hao et al. show that successful expression of factor IX in a hematopoietic cell line can be achieved using the Moloney murine leukemia virus long terminal repeat (vector LIXSN) or the cytomegalovirus promoter (vector LIXCIX) (see paragraph spanning p. 877-888 and Table I). Hao et al. suggests improving on this success using hematopoietic specific promoters (see p. 878, Col. 2, last paragraph and p. 879, Col. 1, first paragraph, and p. 879, Col. 1, lines 27-28). In addition, Uzan et al. teach that the GPIIb promoter directs tissue specific expression in megakaryocytes. Thus, the references combined provide more than an obviousness to try. On the contrary, one of ordinary skill in the art at the time of the invention having the Hao et al. and Uzan et al. references in hand would have had a reasonable expectation of success for the reasons explained above. Moreover, with Hao et al. suggestion to use hematopoietic specific promoters in the production of factor IX, one of

skill in the art would have been motivated to use the GPIIb promoter taught in Uzan et al. because it was shown to be specific for megakaryocytes (a hematopoietic cell).

Applicants argument that Hao et al. concedes that expression in non-transformed cell lines is difficult and therefore one of skill in the art would not have a reasonable expectation of success in transfecting and expressing a DNA construct in a nontransformed hematopoietic cell even if the GPIIb promoter of Uzan et al. is used has been considered but is not deemed persuasive. First, as explained in the previous Office Action, (Paper No. 7, 2nd full paragraph) the claims are not limited to expression in primary cells. Moreover, Applicants have not provided any evidence to support the argument that one of skill in the art would believe that there is an unreasonable expectation of success in expressing factor IX in primary cells using the teachings of Hao et al. and Uzan et al. In this case, Applicant is reminded that the only examples provided in the present specification are drawn to *in vitro* expression in transformed cell lines.

Thus, for the reasons stated above and in the previous Office Actions, the claims appear to be unpatentable over Hao et al. in view of Uzan et al.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al. and Uzan et al. as applied to claims 1-3 and 5-14 above, and further in view of Kurachi et al. (J. Biol. Chem. (1995) 270(10): 5276-5281; cited in IDS of Paper No. 2).

It is noted that this rejection has been reinstated from the Office Action of Paper No. 5. The rejection was withdrawn in Paper No. 7 because the claim was amended to

depend from amended Claim 8 which included the limitation that the cells were platelets (not taught in the prior art references). However, Claim 8 has now been amended to change the limitation from cells that are platelets to cells that are megakaryocytes. As explained above, Uzan et al. suggests that the GPIIb can be used to target expression of heterologous genes in *megakaryocytes*. Thus, the rejection is necessitated by the amendment.

The teachings of Hao et al. and Uzan et al. have been described above.

Hao et al. and Uzan et al. do not teach a DNA construct wherein Intron 1 of the human factor IX gene is inserted into the factor IX cDNA.

Kurachi et al. teach a construct encoding human factor IX wherein the first intron of human factor IX is inserted into the factor IX cDNA and wherein the Intron I sequence enhances transgene expression by protecting spliceosome complexes from random degradation (see abstract and figure 2, p. 5278).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add an Intron I sequence of factor IX to a DNA construct comprising a tissue specific promoter and a sequence coding for factor IX as taught and suggested in Hao et al. and Uzan et al. One would be motivated to insert the Intron I sequence into the factor IX cDNA because, as Kurachi et al. teach, the first intron of Factor IX functions to enhance gene expression. Thus, it appears that the claims are unpatentable over the prior art.

Objections

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 14 adds the limitation that the cells are megakaryocytes. Claim 14 is ultimately dependent from Claim 8 and therefore contains all of the limitations of Claim 8. Thus, since the limitation of claim 8 is that the cells are megakaryocytes, Claim 14 does not further limit the claims from which it depends.

Conclusions

No Claims are allowable.

This application is an RCE. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
December 3, 2002

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600